Interview Summary	Application No.	Applicant(s)	
	10/770,403	MURPHY, TIMOTHY P.	
	Examiner	Art Unit	
	Paul B. Prebilic	3738	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Paul B. Prebilic*. (3)*Adam Cermak*.

(2) *Timothy Murphy*. (4)_____.

Date of Interview: *05 June 2007*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No.
If Yes, brief description: *NIH summary statements for grant applications (see attached)*.

Claim(s) discussed: *all claims generally*.

Identification of prior art discussed: *Ruiz and Flesler as applied in the most recent Office action*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Mr. Cermak and Dr. Murphy presented the NIH statements attached as objective evidence of unobviousness. They plan on filing these papers to make them formally of record when they respond to the Office action. The Examiner thought that this evidence presents a new consideration at this point, but will evaluate any response to the Final rejection according the guidelines in the Manual of Patent Examination Procedure*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Paul B. Prebilic
Primary Examiner

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

_____
Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

SUMMARY STATEMENT
(Privileged Communication) *Release Date:* 04/16/2007

PROGRAM CONTACT:
John Haller
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Application Number: 1 R21 EB007566-01

Principal Investigator

MURPHY, TIMOTHY P MD

Applicant Organization: QUEQUECHAN ENGINEERING, INC.

Review Group: ZEB1 OSR-B (M1)
National Institute of Biomedical Imaging and Bioengineering Special Emphasis Panel

Meeting Date: 03/14/2007
Council: MAY 2007
Requested Start: 07/15/2007

RFA/PA: EB06-003
PCC: AITD

Project Title: Percutaneous mesenteric arterial flow modulation as treatment for morbid obesity

SRG Action: **
Human Subjects: 10-No human subjects involved
Animal Subjects: 30-Vertebrate animals involved - no SRG concerns noted

Project Year	Direct Costs Requested
1	223,060
TOTAL	223,060

**NOTE TO APPLICANT: As part of the initial scientific merit review process, reviewers were asked to identify those applications with the highest scientific merit, generally the top half of applications that they customarily review. At the study section meeting, those applications were discussed and assigned a priority score. All other applications, including this application, did not receive a score. Provided is a compilation of reviewers' comments prepared prior to the meeting, without significant modification or editing by NIH staff.

1R21EB007566-01 MURPHY, TIMOTHY

SCIENTIFIC REVIEW ADMINISTRATOR'S NOTE

DESCRIPTION (provided by applicant): Obesity is an epidemic in the U.S. More than half of the U.S. population is overweight, one-third are obese, and more than 5 million adults in the U.S. are categorized as morbidly obese (body mass index >40). Obesity is associated with increased cardiovascular disease risk and mortality. The BROAD, LONG-TERM OBJECTIVES of this project are to improve health in individuals with morbid obesity. The SPECIFIC AIMS are to test a novel approach at inducing weight loss in an animal model by reducing blood mesenteric arterial blood flow thereby not allowing increases in mesenteric blood flow required for digestion after a large meal, the purpose of which is to result in a behavioral change to avoid over-eating. The RATIONALE is that because blood flow in the mesenteric circulation normally increases 3-fold in diastole (the dominant part of the cardiac cycle) after meals, it should be possible to induce a state where blood flow is adequate to maintain bowel viability without symptoms at rest, but not sufficient to accommodate the large increase in flow that is necessary after meals, resulting in abdominal pain and/or diarrhea after large meals. This will result in behavior changes such as avoidance of eating large amounts, thereby producing weight loss. Mesenteric blood flow modulation will be done by a combination of vascular occlusion of the gastroduodenal artery (GDA) and variable flow reduction of the superior (cranial) mesenteric artery (SMA) in pigs using a proprietary stent-graft designed for this purpose, to be placed using percutaneous interventional techniques. The HEALTH-RELATEDNESS is that weight loss lowers the risk of cardiovascular and other health adverse events, and improves quality of life. If effective, the proposed treatment would be appealing for those who are not candidates for invasive gastric bypass surgery, and may prove to be a lower risk alternative to gastric bypass surgery. The RESEARCH DESIGN AND METHODS would be to develop a fabric-covered vascular stent-graft for percutaneous, fluoroscopically-guided placement into the superior (cranial) mesenteric artery of pigs, and occlusion of the GDA with coils. After the prototype is developed and bench-tested, it will be introduced into 10 adult swine, with 10 also undergoing a sham procedure. Post-procedure course will be monitored including dietary intake and weight up to 2 months. We will look for a statistically significant difference in weight change score as a continuous variable as the primary endpoint, and will also examine adverse events, and daily dietary caloric intake pre- and post-procedure. Principal Investigator: Murphy, Timothy, Patrick More than 5 million adults in the U.S., 5% of the adult population, meet the definition of morbid obesity. There may be as many as 2 million people in the U.S. who would be candidates for the proposed treatment, which may be possible with lower cost and substantially lower morbidity and mortality than gastric bypass surgery.

CRITIQUE 1:

Description: The authors propose to build and investigate a new covered stent with constricted central diameter so as to impose gastric ischemia as a means to treat morbid obesity.

SIGNIFICANCE:
Although obesity is an extremely important national problem, it has primarily behavioral and cultural causes. Nevertheless, the use of a more convenient, cheaper, less invasive procedure such as the authors propose has the potential to replace existing invasive surgical procedures and to enable a larger number of people to be treated with a physical intervention for something that is essentially behavioral in nature. Also as the authors admit there are questions of ethics, purposeful induction of pain, and risks of infarction that arise and they argue that the benefit is worth the risk. There is a question as to how many patients would submit to a procedure to induce ischemia where, as the authors state, "the symptoms of this disease include weight loss, malabsorption, anorexia, food fear, and diarrhea." These somewhat contradictory justifications for the project tend to detract from one's enthusiasm for it in terms of its significance.

APPROACH:
The authors approach is to design, manufacture, and test a PTFE-covered, balloon-expandable stent that upon deployment can have a longitudinally-central diameter restriction to reduce blood flow to the superior mesenteric artery (SMA) and simultaneously to use coils to embolize the gastroduodenal artery (GDA). While the authors should be able to achieve their technical goals of creating such a stent and deploying it in a number of test animals, the design procedure appears to be somewhat of a trial-and-error approach. For a new stent of this kind it would seem that to have any justification for long term efficacy and safety one would have to demonstrate through computer simulations using finite element analysis (FEA) that a particular design could achieve its physical goals. Most covered stents and stents in general are placed in abnormal or diseased vessels so one would be concerned about matching the compliance and other mechanical properties of such a new stent with the normal vessel that it is intended to be deployed in. One is also unconvinced that the procedure as the authors claim is totally reversible by simply balloon expanding the new stent so as to enlarge the central diameter. What started out as a normal healthy vessel will never be as such again and one is uncertain as how such a vessel might react years later if it were desired to undo the treatment because the patient might have matured or may no longer have the behavioral problems that originally caused the obesity. Details of the use of the coils to occlude the GDA were also lacking as well as possible long term results from this apparently irreversible procedure.

It is not even certain that the procedure would necessarily have the desired effects in the intermediate term. If there were collateral blood flow then less ischemia would be induced and there might be minimal effect. If there were minimal collateral flow then the risk of infarction would seem to be greater.

There is also a question as to the experience, expertise, and capability of laser cutting the stents in-house since this usually requires great accuracy and dedicated equipment and personnel. It might be less expensive and more advantageous to contract out the laser cutting to facilities that do only such work and who would return electro-polished sample quantities without the learning curve that the in-house facility would appear to have to go through. Additionally, there is no detailed discussion of a possible special balloon that might be needed to expand this new stent so that the diameters are not uniform. Most existing balloon-expandable stents use a non-compliant balloon to expand stents to a somewhat uniform diameter perhaps with a bit of dog-boning; however, for the stent with constriction in middle as proposed by the authors, either a compliant balloon with difficult to predict final expanded diameter, or a non-compliant specially designed balloon to fit the desired final shape would have be used. In either case there are technical problems that the authors do not seem to have considered in detail.

INNOVATION:
The design of the new stent is somewhat innovative; however, much of the technology they propose for the stent presently exists. The application to purposely create blood flow constriction in a normal vessel appears original.

INVESTIGATORS:
Dr. Timothy Murphy is a prominent vascular interventional radiologist who is a principal in the small company Quequechan and he is the director of Vascular Disease Research at Rhode Island Hospital and on the faculty of Brown University. His commitment is 10%. His experience and credentials would appear to be quite appropriate for the clinical and leadership role he plays in the project. L. Bullock, PhD of U. Mass-Dartmouth is a physicist and manager of the Photonics Lab; however, he has no research publications listed since 1973 in his very brief biosketch. It is stated in the proposal that he had some experience in laser cutting stents at one time but the extent of his capability in FEA and leading the design and manufacture of the stents is hard to evaluate from what is stated in the proposal. Other work is to be done by graduate students, laboratory personnel at Rhode Island Hospital animal facilities, and an administrative assistant to Dr. Murphy.

ENVIRONMENT:

Environment appears adequate to the tasks proposed although there is some question regarding the approach, experience, and perhaps the resources needed to adequately laser cut the stents.

OVERALL EVALUATION:
It would seem that even if the proposed stent were able to be satisfactorily made and deployed, the simple animal experiments envisioned to see if a population of 10 farm pigs can be induced to eat less would be hardly conclusive regarding long term efficacy and safety in humans. There are also some questions regarding the techniques proposed for designing and deploying the new stents with the correctly designed balloons as well as some question about the use of in-house facilities for laser cutting the stents. Basically, the authors propose to induce gastric ischemia by constricting healthy vessels with a permanently deployed stent and with embolic coils. It is difficult to be enthusiastic about a proposal to make more accessible a potentially risky alternate physical treatment for what is essentially the behaviorally-caused condition of obesity.

CRITIQUE 2:

SIGNIFICANCE:
The PI proposes to develop a stent graft that can be placed in the superior mesenteric artery endovascularly under image guidance. The stent graft will be balloon inflatable and when inflated will take on a "dog bone" shape with a stenosis in the center such as to restrict blood to the smaller arteries supplying the bowel. The premise is that by constricting the flow through the superior mesenteric it will create a condition similar to the clinical condition of chronic mesenteric ischemia. Patients with that condition have to adapt their eating habits to the condition by eating small amounts of food frequently and therefore lose weight. Obesity in the US has reached epidemic proportion and approximately $100 billion is spent annually for the treatment of obesity related diseases. Combating obesity is significant.

APPROACH:
The PI proposes two specific aims. In the first aim they will develop a variable diameter stent-graft for introduction in the pig superior mesenteric artery in conjunction with selective embolization of collateral arteries to reduce mesenteric flow. In the second specific aim the device will be placed in a cohort of barnyard swine to compare their weight and caloric intake to a cohort of controls.

The application is essentially proposing to develop a device for a non established animal model and then see if an animal model can be established. What should be done first before embarking on the road of device development is to demonstrate that an animal model exists by using simple coarctations around the mesenteric artery. Also, in the methods section the application does not talk about embolization of collaterals despite the fact that it appears in the first specific aim.

INNOVATION:
BioMEMS Highly innovative application

INVESTIGATORS:
The PI is experienced in endovascular procedures and implantation of stents. The faculty is experiences in the design and fabrication of stents and stent-grafts.

ENVIRONMENT:
The available facilities of the proposing organization and partner are sufficient to execute the proposed project.

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISKS:
N/A

GENDER, MINORITY AND CHILDREN SUBJECTS:
N/A

VERTEBRATE ANIMALS:
No concerns, IACUC approval pending.

BIOHAZARDS:
No concerns

OVERALL EVALUATION:
Strengths: Very innovative proposal, attacking obesity from an unorthodox direction.

Weaknesses: The percent stenosis required for significant flow restriction through the mesentery artery is very high and it is not clear that it can be achieved by varying the stent strut properties alone. There is no established animal model for weight modulation using mesenteric ischemia. The technical challenges in the fabrication of a device that will dialate less than 50% in the center compare to the ends are not laid out and while it is noted that design modifications will be required, solutions are not proposed.

BUDGET:
Reasonable for the amount of work proposed.

CRITIQUE 3:

The stated long-term objective of this application is to improve health in individuals with morbid obesity (Body mass index >40). The specific aims are to test a novel approach at inducing weight loss in pigs by diminishing mesenteric blood flow and inducing an iatrogenic state of mesenteric insufficiency. This is accomplished by percutaneous stent placement into the Superior Mesenteric Artery (SMA) and occluding other arteries selectively by embolization.

Study animals will be compared to animals treated by sham procedure by monitoring dietary intake and weight over two months. Obesity and related medical illness is on the increase in N. America. Bariatric surgery (Gastric Bypass) is an accepted corrective measure in patients who fail tradition weight loss plans and have weight-related co-morbid illness. Minimally invasive alternatives, like the "Lap Band" are also available. Chronic mesenteric ischemia often results in post-prandial discomfort, sidophobia, and weight loss. However, injury or occlusion of the SMA and other mesenteric vessels can result in significant morbidity and mortality. This proposal is IACUC approved. Human subjects approval would require strong pilot data suggesting safety and efficacy.

SCIENTIFIC REVIEW ADMINISTRATOR'S NOTE:

VERTEBRATE ANIMALS (Resume): ACCEPTABLE

NIH announced implementation of Modular Research Grants in the December 18, 1998 issue of the NIH Guide to Grants and Contracts. The main feature of this concept is that grant applications (R01, R03, R21, R15) will request direct costs in $25,000 modules, without budget detail for individual categories. Further information can be obtained from the Modular Grants Web site at http://grants.nih.gov/grants/funding/modular/modular.htm

MEETING ROSTER

National Institute of Biomedical Imaging and Bioengineering Special Emphasis Panel
NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING
ZEB1 OSR-B (M1) R
March 14, 2007 - March 15, 2007

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Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

NOTIFICATION OF SCIENTIFIC REVIEW ACTION

Release Date: 04/16/2007

MURPHY, TIMOTHY P MD
RHODE ISLAND HOSPITAL
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593 EDDY STREET
PROVIDENCE, RI 02903

Our Reference: 1 R21 EB007566-01 ZEB1 OSR-B (M1)

The scientific merit review of your application, referenced above, is complete. As part of this initial review, reviewers were asked to provide written evaluations of each application and to identify those with the highest scientific merit, generally the top half of applications they customarily review, for discussion at the meeting and assignment of a priority score. Your application did not receive a score. Unscored applications are neither routinely reviewed at a second level by a national advisory council or board nor considered for funding.

Enclosed is your summary statement containing the reviewers' comments. You should call the program official listed below to discuss your options and obtain advice.

PROGRAM CONTACT:
John Haller
301-451-4780
hallerj@mail.nih.gov

If you choose to resubmit, it is important to respond specifically to comments in the summary statement, as outlined in the instructions in the PHS 398 application kit (http://grants1.nih.gov/grants/funding/phs398/phs398.html).

Enclosure

cc: Business or institutional official of applicant organization

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SUMMARY STATEMENT
(Privileged Communication)

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v

Release Date: 03/23/2006

Application Number: 1 R41 DK076502-01

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PROVIDENCE, RI 02903

Review Group: ZRG1 DIG-A (10)

Meeting Date: 03/10/2006
Council: MAY 2006
Requested Start: 07/01/2006

RFA/PA: PA06-007
PCC: NCD DDSB
Dual PCC: HHVOVN
Dual IC(s): HL

Project Title: Percutaneous mesenteric arterial flow modulation as treatment for morbid obesity

SRG Action: **
Human Subjects: 10-No human subjects involved
Animal Subjects: 44-Vertebrate animals involved - SRG concerns

Project Year	Direct Costs Requested
1	220,360
TOTAL	220,360

**NOTE TO APPLICANT: As part of the initial scientific merit review process, reviewers were asked to identify those applications with the highest scientific merit, generally the top half of applications that they customarily review. At the study section meeting, those applications were discussed and assigned a priority score. All other applications, including this application, did not receive a score. Provided is a compilation of reviewers' comments prepared prior to the meeting, without significant modification or editing by NIH staff.

BUDGET MODIFICATIONS

1R41DK076502-01 MURPHY, TIMOTHY

CRITIQUE 1:

SIGNIFICANCE: The authors have identified morbid obesity as a clinically important problem for which optimal treatment has not yet been identified. As such, novel treatment methods are needed. The significance of the current proposal is the novel idea which the authors intend to study as a new and different approach to treatment of morbid obesity, that of the induction of visceral ischemia.

APPROACH: Chronic visceral ischemia is a serious condition in which blood flow to the small and large intestine is impaired; usually from atherosclerotic narrowing. Significant occlusion of two of the three visceral arteries (celiac, superior mesenteric, inferior mesenteric) is needed to induce chronic visceral ischemia. Although usually painful stimuli, such as cutting with a knife, or stabbing with a needle do not induce pain in the intestines, the two most powerful inducers of pain are distention and ischemia. In patients with chronic visceral arterial occlusion, blood flow to the intestines can't increase in response to a meal. Mucosal flow comprises 50% of flow to the intestines in the fasting state, and this increases to 75% after a meal. The progression from minor symptoms to transmural infarction is unpredictable and mortality of transmural infarction is 80%.

The inability to increase visceral blood flow and the resultant ischemia in response to a meal creates pain, which in turn causes affected individuals to avoid food, or eat only small amounts – "food fear". Consequently, affected individuals lose weight. It is this aspect that the authors intend to exploit in their admittedly novel approach to the treatment of morbid obesity. Turning conventional therapy on its head, instead of using stents to open narrowed vessels, this proposal seeks to place stents to decrease visceral blood flow, inducing "food fear". The concept of establishing a negative stimulus-response in the morbidly obese is not new, as the pouch restriction and distention in response to overfeeding, or the gas bloat and diarrhea seen after eating too many sweets associated with gastric bypass are similar examples.

There are four aims. The first proposes to create balloon-expandable stents for purposes of this proposal. There is no discussion of why currently existing stents might not work, at least for proof of principle. The authors present *in situ* data for a 30 kg swine that gives the size of the cranial mesenteric artery (analogous to human superior mesenteric artery) as 6 mm outer diameter. It is probably important to know whether in the fed state the proximal artery dilates as well as the downstream vascular bed. Most atherosclerotic lesions are fixed, unlike normal arteries. This could be evaluated *in vivo* with duplex ultrasonography.

Aim 2 is to study mesenteric arterial flow in the swine visceral circulation to understand collateral pathways of importance and devise ways to occlude these pathways. I note that the authors appear to believe that the 6 mm artery in the 30 kg swine is somewhat at the limits of their catheterization abilities, so how small collaterals are likely to be embolized is not clear. There is no plan for obtaining flow data that might suggest how much limitation is necessary to effect the desired weight loss. There are no specific experiments presented to show exactly how the authors intend to satisfy Aim 2.

Aim 3 is to use data supplied from the first two aims to perform a study in which adult swine are randomized to reducing stent or sham catheterization. The randomization is said to be after arteriography, the rationale for which is unclear. They will then observe the animals to see if one group gains more weight. There appear to be 5 swine in each group, however there is no discussion of how these sample sizes were generated. Although maintenance of swine for such a study is resource intensive, a biostatistician should help decide how many should be treated in each group for differences in weight loss. The authors are predicting a 20 pound difference in weight, but there is no rationale for this choice. The 20 pound difference is a delta of one pound per three days. There is no discussion of what signs they will be observing to determine if the swine are in distress (e.g. manifest food fear).

Aim 4 will use tolazoline, an alpha adrenergic blocker, to mimic increased flow associated with a meal. The plan is to first place the stent, then dilate the luminal diameter so the resting pressure across the stent is nil. Then, tolazoline, 25 mg, will be used to see if a pressure gradient can be detected. The authors do not discuss what they intend to do if no gradient can be seen after infusion of the tolazoline.

INNOVATION: This is an innovative idea, and looks at the treatment of morbid obesity in an entirely novel way.

INVESTIGATORS: Appear to have the expertise to carry out the required studies.

ENVIRONMENT: Adequate.

VERTEBRATE ANIMALS: Appears appropriate. As a part of the scientific design, however, more detail on exactly how the investigators will score pain and food aversion must be addressed.

OVERALL EVALUATION: The strength of this application is the novelty of the approach and the stent fabrication expertise of the investigators. Weaknesses include a basic conceptual issue about whether it is ethical to induce pain as an approach to trying to get patients to lose weight. Further, given the significant degree to which arterial occlusion is necessary in humans to get chronic visceral ischemia, it is unclear whether adequate occlusive stenting can be done safely. All issues of translation into the clinical setting aside, for the reasons mentioned above, it is unclear that the swine studies proposed will answer the question of whether or not this is a viable approach.

BUDGET: I question the charge of administrative (secretary/clerical). Otherwise the budget appears adequate.

CRITIQUE 2:

SIGNIFICANCE: Obesity is a significant health problem in the US and worldwide. Therefore, developing new therapeutic modalities for inducing weight loss is a very relevant area of investigation. However, in this application the PI is proposing to introduce a stent into the arterial blood vessels of the small intestine to induce a serious condition resembling chronic intestinal ischemia. This approach is likely unfeasible and unethical.

APPROACH: This is the first submission of an R41 STIR application to develop a new treatment modality for obesity based upon reducing blood flow to the small intestine. The approach this investigator is taking to address this important issue is seriously flawed since the PI is effectively suggesting the induction of a serious disease state, i.e., chronic abdominal angina and mesenteric ischemia to induce weight loss. Thus, the weight loss will derive from the pathological condition associated with severe symptoms in many cases, including diarrhea, malabsorption and significant abdominal pain. How would one control for the amount of ischemia generated in the small intestine to avoid, for example, intestinal infarction? Unfortunately the PI has not discussed any of these important issues related to the applicability of this methodology to the human condition within the experimental design of this application.

INNOVATION: This proposal is certainly innovative; however, it is unlikely to be applicable to obese patients without serious complications.

INVESTIGATORS: Dr. Murphy is a professor of research at Brown Medical School. He is an established investigator in the field of vascular biology, with expertise in vascular stenting. He is collaborating with Quechan Engineering, Inc. It is unclear from the proposal who in this company is collaborating in these studies. Dr. Murphy is certainly qualified to perform these studies.

ENVIRONMENT: Appropriate as described.

VERTEBRATE ANIMALS: The five points that are required for vertebrate animals are not appropriately described.

OVERALL EVALUATION: This is a new R41 STIR application to develop a novel therapeutic modality to treat obesity. The main problem with this grant proposal is that the PI is proposing to induce a serious disease state in obese patients to cause them to fear food, experience serious symptoms of intestinal ischemia and then lose weight. This proposal raises significant ethical concerns and there is highly unfeasible. Therefore, the proposal is not recommended for further consideration.

BUDGET: Appropriate as described.

CRITIQUE 3:

SIGNIFICANCE: Morbid obesity is a significant public health problem and is responsible for placing an enormous financial burden on our society. It is also a major risk factor for cardiovascular diseases and diabetes. The main therapy against obesity consists of various weight-loss programs based on stimulating exercise and restricting dietary intake. Other more radical treatments are surgically based and include gastric bypass. Such treatments are not free of complications (1-2 % mortality) and are generally reserved for the most severely obese patients. The investigators propose a radically new method based on well-known endovascular techniques used commonly to treat patients with vascular diseases. This approach, placing a stent-graft in the superior mesenteric artery to reduce blood flow and thus create a controlled form of mesenteric ischemia, is somewhat innovative and if successful could prove quite significant despite a number of major problems and ethical consideration.

APPROACH: The goal of the proposal is to induce a "controlled" form of mesenteric ischemia by placing a stent-graft in the superior mesenteric artery in order to limit food intake. The resultant "food fear" would force obese patients to eat small meals to avoid causing excruciating abdominal pain due to the newly created mesenteric ischemia. There are a number of major problems with this proposal:

Stent graft design: There are a number of commercially available stents and stent grafts, yet the investigators do not provide any explanation as to why they need to design a new type of stent, especially in view of the fact that such stent grafts have been used for the same purpose (i.e. reducing blood flow) in the case of Transjugular Portosystemic Shunts (TIPS) for patients with portal hypertension. The same dumbbell shape that the investigators want to test to induce mesenteric ischemia has already been used successfully with commercially available stent grafts to reduce porto-systemic venous flow. The rationale for a new stent design must be provided.

Experimental protocol: The need for randomization after the diagnostic angiogram is not explained and does not appear justified unless it is done to control for the effects of the surgery.

Unexplained potential problems: No remedy to potential problems encountered during the conduct of the proposed experiments is given. For example, what if the stent graft does not reduce blood flow enough? Or if on the contrary, the stent graft is too occlusive, which can happen in vessels of that size (6 mm)? The problem of distal flow is not addressed at all. Not only does it have practical implications from the standpoint of successfully completing the experiments, but it does also have major ethical considerations if the degree of flow reduction can not be totally controlled. It could lead to irreversible ischemia requiring some form of surgical intervention if at all.

Ethics: There should be serious reservations about conducting the proposed experiments in pigs given the fact that evaluating and quantifying the degree of mesenteric ischemia-related pain and "food fear" is not addressed at all by the investigators. It might not be feasible to do so, but at the very least the investigators should have studied that problem in detail. Translating this method to humans is even more problematic from the ethical standpoint. How can we justify inducing severe abdominal pain every

time someone eats? Furthermore, the problem of irreversibility i.e. in case the pain is intolerable for the patient, is not addressed at all.

INNOVATION: The concept of treating morbid obesity via endovascular means is highly innovative, although it is extremely controversial ethically. However, the use of stents or stent-grafts as in this case to limit flow in a vascular structure is not new as it has been used not uncommonly for patients suffering from portal hypertension treated with Transjugular Portosystemic Shunts (TIPS). Some of these patients can experience a high degree of encephalopathy as a result of increased flow from the portal vein to the hepatic veins. In such instances (published reports by Haskal), a stent-graft can be shaped as described in the current protocol in order to reduce blood flow without causing complete occlusion.

INVESTIGATORS: The PI is a well respected interventional radiologist with a vast experience in the field of peripheral vascular interventions. His team should be able to accomplish some of their goals, especially the creation of a stent graft, but it is not sure whether the remaining goals will be achieved.

ENVIRONMENT: Appropriate for the scope of the studies described in the proposal.

VERTEBRATE ANIMALS: Serious reservations about the experimental design of the study involving the animals, specifically Aims 2-4. No explanation is provided to justify the number of animals in terms of reaching statistical significance. The investigators did not address how they will evaluate mesenteric ischemic pain or quantify food fear in the pigs. Measuring weight loss is perhaps scientifically relevant but certainly not ethically correct. This must be dealt with in some fashion. The proposal has not yet been submitted to ACUC.

BIOHAZARDS: No issue.

OVERALL EVALUATION: Although this proposal deals with a critically important issue plaguing our health care system, namely obesity and more specifically morbid obesity, it is far from convincing from the scientific standpoint. The notion of using endovascular minimally invasive techniques to create a "controlled" form of mesenteric ischemia to reduce food intake through induction of food fear may be innovative but it is largely untested and the proposal is filled with unanswered questions that may prove to be insurmountable. The experimental design is also generally weak and potential problems are not dealt with appropriately.

BUDGET: Appropriate except the 50% salary support for an administrative secretary, as it does not appear clear at all what the need for this person will be throughout the work proposed in this application.

MEETING ROSTER

Center for Scientific Review Special Emphasis Panel
CENTER FOR SCIENTIFIC REVIEW
ZRG1 DIG-A (10) B
March 10, 2006

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NOTIFICATION OF SCIENTIFIC REVIEW ACTION

Release Date: 03/23/2006

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Our Reference: 1 R41 DK076502-01 ZRG1 DIG-A (10)

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Christine Densmore
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densmorec@extra.niddk.nih.gov

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Enclosure

cc: Business or institutional official of applicant organization

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